Articles

Varicella During Pregnancy
Maternal and Fetal Effects

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To determine the characteristics of maternal varicella at our institution, we reviewed all cases of primary varicella in pregnancy. Using a perinatal database that summarizes all obstetric admissions, we reviewed the medical records of women with varicella infections during pregnancy. Over a 5½-year period, 31 pregnancies were affected by varicella infection among 11,753 deliveries. The mean age of those patients was 19.6 years, significantly different from our overall population of 25.3 years ($P < .05$). The racial composition of 35% Hispanic, 35% white, and 29% African American was different from that of our general population of 55% white, 38% African American, and 6% Hispanic ($P = .023$). The mean gestational age of the eruption of vesicles was 25 weeks. Of the 31 women, 7 had preterm labor within a week of their varicella, 3 delivered prematurely, and 3 infants had a birth weight of less than 2,700 grams. Respiratory symptoms developed in 6 women, and pneumonia developed in 4, 2 of whom required ventilatory support, 1 for 5 days, the other for 49 days. Eight women received acyclovir during gestation, and none suffered sequelae. In all, 6 infants had lesions and anomalies noted at birth, 5 possibly associated with varicella.

Varicella infection is associated with a greater-than-expected level of both maternal and fetal morbidity. The fetal disease may occur due to maternal infection at any gestation and is most likely a spectrum of complications. The maternal disease appears to be worse in the latter half of pregnancy. Programs of prevention through vaccination must account for a possibly decreased level of immunity in different populations.

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Varicella infection in pregnancy has possibly devastating consequences for both women and their fetus. The overall incidence of varicella in pregnancy has been estimated from 1 to 5 per 10,000.[1,2] Although it is a relatively benign disease in early childhood, the complications, both fetal and maternal, present several management problems for clinicians. Several issues regarding varicella in pregnancy are still debated, such as the spectrum and degree of fetal manifestations, the incidence and severity of varicella pneumonia, and the use of antiviral agents. Some authors have suggested that the rate of fetal manifestations is low if the maternal infection occurs more than a week from delivery, whereas others have reported a wide spectrum of fetal involvement.[3] The use of varicella-zoster immune globulin vaccine for chickenpox when maternal infection occurs within five days of delivery is an established practice, but the effectiveness of its use in preventing fetal disease is incomplete at best.[1,4] The use of acyclovir for the treatment of maternal chickenpox is also an area of discussion. Some investigators recommend treatment of any pregnant patient with varicella, but others recommend using the drug only for varicella pneumonia.[2,5-8] Data are incomplete as to the use and indications of antiviral agents. Recent admissions to our obstetric service of women with chickenpox and its subsequent morbidity led us to review the effects of this disease during pregnancy.

Patients and Methods

We reviewed the medical records for the period January 1989 through July 1994 of all patients admitted to the obstetric service at the University of North Carolina Hospital, Chapel Hill, both delivered and undelivered, who had chickenpox in pregnancy. All diagnoses were made clinically. The University Hospital is a tertiary-level referral center that cares for both a public and private population. It is the policy of the University Hospitals that all pregnant women be admitted to the obstetric service regardless of diagnosis. On discharge from the hospital, all obstetric patients' records are evaluated by a specially trained obstetric technician who records them in the perinatal database. All records are then reviewed by a senior perinatologist. Varicella is coded for specifically. Thus, if a woman had chickenpox

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in pregnancy, even if she was not admitted for that diagnosis, the event would be noted and her medical record could be retrieved.

Using a MEDLINE search with manual cross-reference, we reviewed recent literature regarding varicella, zoster, and chickenpox infections in pregnancy. Statistical analysis was performed with Fisher's exact test and *t* test with unequal variance. A *P* value of less than .05 was considered significant.

Results

From January 1989 through July 1994, there were 31 cases of pregnancy complicated by chickenpox infection on our obstetric service (Table 1). There were 32 live-born infants delivered (1 set of twins) and no cases of fetal demise. During this time period, 11,753 women were brought to delivery. Of the 31 women with chickenpox, 3 were referred from other institutions and 4 women delivered at other hospitals. The mean age of patients was 19.6 years ± 4.3 (1 standard deviation; range, 15 to 33 years).

Chickenpox developed in 11 women at 24 weeks or less. The mean date of delivery was 39 weeks (range, 35 to 42 weeks). Four women had delivery at less than 37 weeks. All four of these patients delivered within a week of the eruption of vesicles. Of the 32 infants, 3 had birth weights of less than 2,700 grams, and 3 infants had birth weights of less than the 10th percentile for their gestational ages. Two of the mothers of these three small-for-gestational-age infants had prenatal care starting late in their pregnancy: 19 and 27 weeks' gestation. The other had no specific risk factors for premature delivery. The smallest infant was 2,500 grams at 41-plus weeks. Three infants received acyclovir at birth for 14 days of therapy. The contacts for infection were documented in 10 of 31 patients, and all but 1 of the contacts were immediate family members.

Other than the preterm deliveries, five women had obstetric complications. There were three cases of preterm labor successfully managed with tocolysis. All three of the preterm labor episodes occurred within a week of the eruption of vesicles, and none of these women had histories of preterm labor. Thus, 7 of the 20 women (35%) who had infection after 24 weeks had preterm labor associated with their varicella. Although the rate of preterm labor in our population is 15.2%, we cannot compare the rates because of the referral nature of our population at a tertiary-care center. Another woman (3%) had third-trimester bleeding not related temporally to her chickenpox; 1% of our population has third-trimester bleeding. Preeclampsia developed in one woman, also distant from her varicella infection; 7% of our population is diagnosed with preeclampsia. We do not think that these last two complications were related to the varicella infections.

Of the 31 women, 6 had respiratory symptoms. Two women had dry coughs, symptoms of chest tightness, and mild tachypnea. They had no evidence of pneumonic involvement on chest x-ray films, and both had normal arterial blood gas measurements. One of the women was administered intravenous acyclovir for seven days, and the other was managed expectantly. Two other women had chest film findings suspicious for varicella pneumonia, in addition to having nonproductive coughs. Respiratory compromise did not develop in either of these patients, and after inpatient observation, both were discharged to home without sequelae. One of these women was treated for seven days with the administration of intravenous acyclovir. Severe varicella pneumonia developed in two patients, with morbid courses. The first, who was carrying a twin gestation at 23 weeks, had shortness of breath and tachypnea five days after the onset of her viral eruption. Intravenous acyclovir therapy was started, but her pulmonary status deteriorated and she required ventilatory support. She remained on a ventilator for five days and was an inpatient for 16 days. Her pulmonary recovery was unremarkable, and her twins were delivered at 38 weeks, appropriately grown and without evidence of congenital varicella.

TABLE 1.—*Demographic Characteristics of the Overall Obstetric Population Compared With Women With Varicella Infection, January 1989 to July 1994*

Demographics	Overall Obstetric Population, % (n=11,753)	Pregnant Women With Varicella Infection, %* (n=31)
Mean age, yr†	25.3 ± 6.2‡	19.6 ± 4.3
Ethnic association†		
Hispanic	6	35
White	53	35
African American	38	29
Parity		
Nulliparous	45	52

*Incidence, 2.6/1,000 pregnancies.
†$P < .05$.
‡Numbers are ±1 standard deviation.

The last patient, a 25-year-old gravida 3 para 1, had a varicella rash develop at 16 weeks of gestation. Her shortness of breath evolved 36 hours after the appearance of vesicles. The patient's respiratory status rapidly declined, and she was intubated four hours after admission. While receiving 100% oxygen before intubation, the patient's Po_2 was 70 mm of mercury, Pco_2 32 mm of mercury, pH 7.37, respiratory rate 48 breaths per minute, and saturation 94%. Treatment with intravenous acyclovir was begun, and a dopamine drip was initiated 24 hours later for decreased urine output. Secondary adult respiratory distress syndrome developed, requiring high ventilator settings. The patient continued to have a fraction of inspired oxygen of greater than 85% for four weeks. A tracheostomy was done at week 4. During the patient's second week on a respirator, staphylococcal sepsis developed, and in her fifth week in the hospital, *Pseudomonas aeruginosa* sepsis developed. Both were managed successfully with antibiotic therapy. She required 13 chest tubes for the treatment of persistent

and recurrent pneumothoraces. Parenteral nutrition was given from 18 to 25 weeks' gestation. The patient was gradually weaned off the ventilator and extubated on hospital day 49. The tracheostomy was capped on day 66. The patient was walking without oxygen by day 70. She gradually recovered as an outpatient, and at 37½ weeks, a 6-lb 8-oz male infant was delivered. Although the infant had no skin lesions or evidence of central nervous system involvement, he did have bilateral clubfeet.

Of the 31 women, 8 received acyclovir, and 2 other women received zoster immune globulin. One woman was given both. None of the 10 women had adverse reactions from these drugs. Of the 32 infants, 6 (19%) had anomalies. Two infants had skin lesions—old and new vesicles—at delivery, none with associated limb lesions or skin scarring. The maternal chickenpox in these cases occurred at 34 and 38 weeks' gestation, and one woman received zoster immune globulin during her infection. One infant (mentioned earlier) had bilateral clubfeet with maternal infection diagnosed at 16 weeks. One infant had meningomyelocele and hydrocephalus; maternal infection occurred at 25 weeks. One had a ventricular septal defect with a patent ductus arteriosus, necessitating neonatal digoxin therapy. This infant's mother had varicella at 20 weeks. The last infant had chronic respiratory difficulties for the first few months of life, characterized as a reactive airways syndrome. The mother of this infant had chickenpox at 24 weeks' gestation and was treated with acyclovir.

Discussion

Several major issues need consideration in cases of varicella in pregnancy: the effects of chickenpox on the pregnancy; the incidence and severity of varicella pneumonia; the treatment and prevention of varicella infection in pregnancy, particularly with acyclovir; and the effects of the infection on the fetus. These issues, although the subject of several reports and data sets, are still under discussion.

Our series and others in the literature indicate that chickenpox has a detrimental effect on pregnancy outcome. Seven women went into preterm labor within a week of their infection, although only four delivered premature infants. These women had varicella infections late in the third trimester. In another report of 43 women with varicella during pregnancy, 4 went into labor prematurely.[8] In a recent multicenter series of 106 pregnant women with varicella compared with age-matched controls, it was also found that the incidence of premature birth was substantially increased among women with chickenpox.[9]

Other authors have also reported cases of preterm labor and delivery associated with chickenpox.[6,10] The mechanism of the increased prevalence of preterm labor is unknown. It is tempting to speculate on the production of inflammatory mediators due to the viremia as being related to the preterm labor, given recent reports of the association of intrauterine cytokines and premature labor. We found at least one other report of a case of abruption in association with chickenpox.[4]

Several authors have suggested that either patients with chickenpox may have a greater predilection of pneumonia developing, or if pneumonia develops, it is more severe during pregnancy.[2,11-13] Others dispute this and feel there is not an increased incidence of pneumonia.[5] In our series, the incidence was 13% (4 of 31). Other authors report incidences of varicella pneumonia between 9% and 16%.[9,14,15] There are many reports of fatal varicella pneumonia occurring in all trimesters. It appears that pneumonia developing later in gestation, particularly in the third trimester, carries the highest mortality.[2,11,16] Of the four cases of varicella pneumonia in our series, the two patients requiring ventilation were in their second trimester. In 1968, 18 cases of varicella pneumonia in pregnancy were reported; it was this report that first noted the severe prognosis of varicella pneumonia in pregnancy.[14] In a review of 21 pregnancies complicated by varicella pneumonia, 12 women required ventilatory support, and 3 died.[2] In two reviews, one of 28 cases and another of 43, both described the need for ventilatory support; some cases were fatal.[8,11] In these and other reports, the authors suggested that there is an approximate maternal mortality of 40% with varicella pneumonia and recommended the use of intravenous acyclovir, suggesting that this may decrease maternal morbidity and mortality.[12] Although our data do not indicate whether pregnant women are at more risk for pneumonia developing, we agree with most authors that when pneumonia develops, it is more severe than in nonpregnant adults.

Nonvaricella pneumonia during pregnancy may also carry a higher morbidity and mortality compared with that in nonpregnant women.[17,18] The graver prognosis may be due to physiologic changes in immunity, altered pulmonary function, and fluid volume shifts during pregnancy. Many of the cases reported in the literature involve the development of the adult respiratory distress syndrome.

Most investigators concur that the use of intravenous acyclovir sodium, 10 to 15 mg per kg a day, is helpful in the management of varicella pneumonia. A higher dose of acyclovir is needed for varicella infection versus herpes simplex because the varicella virus is ten times less sensitive than herpes simplex to the effects of acyclovir.[15] Acyclovir inhibits viral DNA polymerase that is common to all the herpesviruses.[15,19] The major side effects from acyclovir are gastrointestinal upset, nausea, vomiting, and a potential for nephrotoxicity.[5,15,19] None of our patients, and few patients in the literature, have experienced difficulties with acyclovir.[6,20] Its safety is well documented for use in pregnancy, and it does not appear to be teratogenic. We support the position that in any pregnant patient with respiratory symptoms and chickenpox, treatment with acyclovir should be promptly started.

Currently, however, there is no published evidence that the use of acyclovir improves the outcome of

patients with uncomplicated chickenpox.[20] Chickenpox pneumonia is extremely contagious. Thus, when possible, our patients who were admitted to the hospital were put in negative-pressure rooms. Such rooms are certainly not easily available on obstetric wards and particularly in labor and delivery suites.

Our patient population appears fairly representative of that of the southeastern United States. Although 85% to 95% of adults in the United States are immune to varicella, the growing population of Hispanic women in the United States may create a larger proportion of patients susceptible to this disease.[9,11] This finding has public health implications. Other authors have suggested an increased susceptibility to varicella in adults from subtropical areas.[1] It is important that foreign-born persons residing in the United States, as well as recent immigrants, be included if varicella vaccination programs are to be effective.

Although the incidence of varicella in pregnancy has been estimated to be 1 to 5 per 10,000 women,[1,2] we are unsure why our incidence was approximately six times higher. Our higher incidence is only partially explained by referrals from other hospitals—3 of the 31 women. Larger, multi-institutional databases may better explain this finding.

The effects of varicella on the fetus is an area of concern.[9] The fetal involvement has been traditionally divided into three forms: "varicella embryopathy" stemming from maternal disease occurring before 20 weeks' gestation; congenital varicella resulting from maternal infection from 20 weeks' gestation until term, but more commonly close to term; and neonatal disease occurring when the pregnant patient has active lesions around the time of delivery. Varicella embryopathy was first described by Laforet and Lynch in 1947 and redefined by several authors since.[21-25] The embryopathy includes limb hypoplasia, skin scarring, central nervous system involvement, and other skeletal lesions.[22-25] Although it is most common before 20 weeks' gestation, the embryopathy has been reported from infection as late as 26 weeks.[3,26]

The largest series of congenital varicella was published recently.[27] In that report, 1,373 pregnancies from 1980 to 1993 in the United Kingdom and Germany were evaluated. The authors found that fetal disease occurred most commonly between 13 and 20 weeks. Fetal anomalies varied from skin lesions to lethal multiorgan system involvement. The use of zoster immune globulin in a pregnant woman may not eliminate the incidence of varicella embryopathy, but if given before maternal infection develops, it may decrease or attenuate fetal disease.[27] The incidence of embryopathy appears to be between 2% and 3%.[1,9,27] Investigators have emphasized that central nervous system involvement from the varicella may lead to deafness, cataracts, chorioretinitis, and microcephaly.[1,3,22]

If we define the embryopathy strictly as limb hypoplasia, skin scarring, and central nervous system lesions, there appears to be a low incidence of infection, less than 3%.[1,9,27] More likely the spectrum of viral manifestations is wider and merges with the syndrome referred to as congenital varicella. Congenital varicella may include skin, limb, and central nervous system effects, but also includes organ involvement such as blood, liver, and spleen.[1,3,22-24,27,28] It may manifest itself as a fulminant neonatal disease with maternal disease in the third trimester or with maternal infection remote from term.[3,24-25,27,28] In a recent review, it was emphasized that the wide spectrum of clinical manifestations in a neonate from maternal varicella included bowel obstruction, urinary tract anomalies, and microtia.[3]

Perhaps the most interesting aspect of congenital varicella is a theory advanced by Higa and co-workers.[28] These authors have postulated that the skin lesions, limb defects, and central nervous system lesions represent zoster infections in utero and that the fetal effects of varicella embryopathy are sequelae of repeated zoster infections in the fetus, including in utero encephalitis. This would explain many of the types of lesions and also the frequent appearance of active vesicles when children are born. Some infants with exposure to varicella during gestation will have no lesions at birth, but zoster will develop in the first two years of life, some will be born with skin scarring, and others will have active lesions.[3,27-29] This theory also explains why the embryopathy initially thought to occur before 20 weeks' gestation has been reported at much later gestations. The theory also links the specific anomalies seen with the embryopathy with the spectrum of lesions seen with the congenital varicella syndrome. Among our patients, it is unlikely that the lesion in the infant with an open neural tube defect was related to the mother's chickenpox. It is difficult to find an association between the varicella infection and the infant with reactive airways disease. Clubfeet and ventricular septal defects have been previously associated with maternal varicella infection,[3,27] but these lesions are common.

It is difficult to draw controls from our population because of the high referral rate of antepartum-diagnosed anomalies at our institution. Data from historical controls yield incidences of as much as 1.2 and 2.5 per 1,000 live births, respectively.[30] Similarly, hydrocephalus, meningocele, and patent ductus arteriosus are not uncommon. Without direct virologic evidence of varicella infection in the infants, we cannot say that there is a causal relationship between an anomaly and a maternal disease. Overall, in our series, 4 of 32 infants had lesions. We agree that pure varicella embryopathy is uncommon. We also concur with Higa and associates that fetal disease is a spectrum and that infection after 20 weeks' gestation is not always benign.

Congenital varicella has been diagnosed antenatally by ultrasound examination.[31] Cranial anomalies, polyhydramnios, hydrops, hyperechoic liver, hydronephrosis, and clubfeet have all been visualized sonographically. Prenatal diagnosis by umbilical blood sampling for immunoglobulin M and polymerase chain reaction for virus has also been reported.[32] It is important to note that

documented fetal infection does not necessarily mean there will be fetal defects.[8]

Many clinicians are under the impression that zoster immune globulin is effective for preventing chickenpox in infants. It is given to an infant when its mother has chickenpox within five days of delivery because there is not sufficient time for immunity to develop and to be transferred to the neonate. Varicella-zoster immune globulin in the dose of 125 U per 10 kg is only 50% effective in preventing the disease, although it may decrease overall severity.[1] There are many reports in the literature of chickenpox and congenital varicella, sometimes fatal, developing in infants despite the appropriate use of this immunizing agent.[1,4,33] Some authors have recommended increasing the dose to 250 U per 10 kg for neonates because of the numerous reported failures with 125 units.[34,35] Varicella-zoster immune globulin is not indicated for pregnant women after varicella lesions develop. Because of problems of obtaining titers in a timely way and the general immunity in the population, we do not routinely give this drug to a pregnant woman after exposure to chickenpox. If a pregnant woman has a known lack of immunity, however, its use would be an appropriate treatment after exposure. Varicella vaccine may be an important and worthwhile solution to the problems of this disease, but it should not be given during pregnancy.

Our series supports the findings of previous reviews that emphasize the severity of chickenpox in pregnancy, particularly the morbidity of varicella pneumonia. It also confirms the association of chickenpox with premature labor and delivery. The definition of varicella embryopathy may be too restrictive; congenital varicella may be a more appropriate term. Programs for preventing both maternal and fetal disease are the next logical step in our approach to varicella in pregnancy.

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